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Abstract

Objective To describe demographic and hormonal characteristics, comorbidities (diabetes mellitus and hypertension), therapeutic procedures and their effectiveness, as well as predictors of morbidity and mortality in a nationwide survey of Italian acromegalic patients.

Design Retrospective multicenter epidemiological study endorsed by the Italian Society of Endocrinology and performed in 24 tertiary referral Italian centers. The mean follow-up time was 120 months.

Results A total of 1512 patients, 41% male, mean age: 45±13 years, mean GH: 31±37 μg/l, IGF1: 744±318 ng/ml, were included. Diabetes mellitus was reported in 16% of cases and hypertension in 33%. Older age and higher IGF1 levels at diagnosis were significant predictors of diabetes and hypertension. At the last follow-up, 65% of patients had a controlled disease, of whom 55% were off medical therapy. Observed deaths were 61, with a standardized mortality ratio of 1.13 95% (confidence interval (CI): 0.87–1.46). Mortality was significantly higher in the patients with persistently active disease (1.93; 95% CI: 1.34–2.70). Main causes of death were vascular diseases and malignancies with similar prevalence. A multivariate analysis showed that older age, higher GH at the last follow-up, higher IGF1 levels at diagnosis, malignancy, and radiotherapy were independent predictors of mortality.

Conclusions Pretreatment IGF1 levels are important predictors of morbidity and mortality in acromegaly. The full hormonal control of the disease, nowadays reached in the majority of patients with modern management, reduces greatly the disease-related mortality.

Introduction

Acromegaly is a serious and disfiguring rare disease, resulting from chronic exposure to elevated GH and IGF1 concentrations, mostly due to a pituitary GH-secreting adenoma.

Almost all the epidemiological studies reported that acromegaly is associated with increased mortality with respect to the general population, mostly due to cardiovascular events and stroke (1, 2, 3, 4). Some (1, 5, 6, 7), but not all the surveys (8, 9, 10, 11), also showed an increased mortality for respiratory complications, and even more controversial are the findings about increased mortality for cancer (4, 12, 13).

Studies published between 1970 and 1995 reported standardized mortality ratio (SMR) of 1.89–3.31, but more recent surveys showed SMR ranging from 1.16 to 2.14 (3, 4). These data were interpreted to reflect an improvement of treatment modalities achieved over the years with the introduction of new drugs (2, 3, 4). Conventional external radiotherapy was found to decrease survival mostly in female patients according to some (7, 9, 11) but not all the studies (3, 6, 10).

All the surveys agree that post treatment GH levels are the strongest outcome predictors (1, 3, 6, 7, 8, 9, 10, 11, 13), but less agreement exists on the role of IGF1 concentrations either at diagnosis or after treatment (8, 9, 10, 11, 13, 14). Since GH and IGF1 act on a wide range of biochemical pathways and modulate intermediate metabolism and cell growth, it is not surprising that acromegaly is a systemic disease, associated with a number of comorbidities. Hypertension is reported to be present in 17–51% and diabetes mellitus in 9–23% of patients (15) contributing to increased mortality (5, 12, 13), whereas a better control of these associated conditions could increase survival (2).

Thus, an increased mortality in acromegaly depends on several factors, some of which changed over the years. Due to the low prevalence of acromegaly, of about 60 patients per million inhabitants (15), only nationwide surveys may produce significant data on patient outcome and predictive factors. This study presents epidemiological data on a large population of Italian acromegalic patients followed up for more than 10 years, and includes mostly patients treated after the introduction of somatostatin analogs (SSAs). The survey has the following aims: i) to describe the demographic, clinical, and hormonal characteristics of this well-defined acromegalic population; ii) to evaluate the kind of therapies preferred by Italian endocrinologists and their effectiveness; and iii) to assess the long-term outcome of the disease and what factors were predictive of morbidity and mortality. To the best of our knowledge, this is the first large-scale epidemiological study on acromegaly in Italy.

Materials and methods

Study design

All the major endocrinological centers in Italy were invited to participate in the survey that was endorsed by the Italian Society of Endocrinology. Twenty-four tertiary referral centers, most of which were University Hospitals, accepted to participate in the study and collected clinical and biochemical data of all acromegalic patients who were proactively followed at the center. The number of patients from each center ranged from 19 to 185 (Fig. 1).

Inclusion criteria were age at diagnosis >18 years, Italian residence and diagnosis of acromegaly made between 1 January 1980 and 31 December 2002 according to standard biochemical criteria at

the time of enrollment, with at least 1-year follow-up after diagnosis. Patients with GH hypersecretion due to ectopic GHRH secretion and multiple endocrine neoplasia type 1 were excluded. The mean follow-up time from diagnosis to the end of the study was 120 months (median: 90 months; interquartile range (IQR): 42–170 months). Data were collected retrospectively by local investigators in a computerized database form developed using Access 2000 software (Microsoft Corporation 1999) and approved by all participants. Periodic meetings were organized in order to make the recording process as homogeneous as possible for all centers. All patients had given their informed consent to the collection of their data according to ethic committee indications of each center. Patients' demographics, estimated date of appearance of typical clinical signs (i.e. change in shoes size, need to have rings enlarged, and coarsening of facial features), pituitary imaging (tumor size and extension), and hormonal data at baseline and during the follow-up period (serum GH levels, serum IGF1 levels, associated hypersecretions, and pituitary deficiencies) were collected for each patient. Diabetes mellitus and hypertension were investigated in order to study their impact on mortality. Hypertension was diagnosed by the presence of systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive therapy. Diabetes mellitus was established on accepted international diagnostic criteria at the moment of diagnosis or use of specific drugs. In addition, the occurrence of cardio- and cerebrovascular events and malignancies during the follow-up was reported. After treatment, acromegalic disease was considered controlled when basal GH (mean of at least three samples) levels were below 2.5 μg/l, and/or nadir GH after an oral glucose load was <1 μg/l, and circulating IGF1 levels were normal according to an age-adjusted normal range (16). The causes of death were obtained from death certificates or medical records. Data on mortality, sex- and age-adjusted distribution of diabetes, and hypertension were then compared with those of the general Italian population using data reported by the Italian National Institute of Statistic (Health of All – Italia, available at: *http://www.istat.it/sanita/Health*), in the year 2008 for mortality and 2005 for prevalence of comorbidities.

Methods

GH and IGF1 assays have changed over the years and were different among the participant centers. The IGF1 values were compared with an appropriate age-adjusted range and expressed also as SDS using the following formula: (IGF1 value−50th percentile)/(97th percentile−3rd percentile) divided by the corresponding *z*-score. Data collected at the end of the 1990s by the University of Genoa (Prof. M Minuto and A Barreca) from more than 4000 Italian normal subjects of different regions, from 0 to 100 years, and including a minimum of 50 subjects for every 5 years of age, served as reference range (17). In particular, for the purpose of the present study, the following normal ranges (3–97th centiles) were used: 18–20 years: 69–736 ng/ml; 21–25 years: 72–415 ng/ml; 26–30 years: 76–378 ng/ml; 31–35 years: 98–318 ng/ml; 36–40 years: 60–280 ng/ml; 41–45 years: 77–260 ng/ml; 46–50 years: 68–286 ng/ml; 51–55 years: 63–252 ng/ml; 55–60 years: 62–263 ng/ml; 61–65 years: 62–241 ng/ml; 66–70 years: 40–201 ng/ml; 71–75 years: 41–217 ng/ml; 76–80 years: 29–269 ng/ml; and 81–85 years: 25–264 ng/ml.

The choice to use a large unique Italian normative database, although offering some advantages, has self-evident important limitations due to variability in IGF1 reference ranges in the many assays used in different centers over the years, and could constitute a bias.

Statistical analysis

Data were expressed as the mean±s.d. and/or as the median and IQR: 25–75%, as appropriate.

Prevalence of diabetes mellitus and hypertension in acromegalic patients was compared with data of the Italian population using direct standardization method and data reported by the Italian National Institute of Statistic in the year 2005. Standardized rates along with 95% confidence interval (CI), which was computed using the Armitage–Berry method, were reported.

Mortality from all causes was compared with the mortality of the Italian population by means of SMR, that is, the ratio of the observed number of deaths in the study sample to the number of deaths expected according to a set of reference mortality rates, adjusted for age, sex, and calendar year. An SMR >1 means a higher mortality than expected in the reference population. Finally, exact Poisson 95% CIs were calculated.

The individual effect of demographic and clinical variables on the risk of developing diabetes mellitus, hypertension, and mortality was evaluated by a logistic regression model. Univariate estimates of the odds ratios were presented along with their lower and upper 95% CIs. Lastly, a multivariate model was built using backward selection including all variables that were found to be significant on univariate analysis. Interactions among variables were also checked. Model evaluation was carried out using a graphical examination of the residual diagnostics. Analyses were performed using R version 2.11.

Results

Population at baseline

A total of 1512 patients, 624 (41.2%) men and 888 (58.8%) women, were included in the study. The mean age at the time of diagnosis was 45±13 years (median: 46 years; IQR: 36–54 years). Male patients were significantly younger than female patients (43±13 vs 47±13 years, $P<0.001$) (Fig. 2). Seventy percent of patients were diagnosed between 1990 and 2002.

Estimated duration of the disease prior to diagnosis was 74 months (median: 60 months; IQR: 36–96) without significant differences between the two genders.

Radiological imaging revealed a microadenoma in 30% and a macroadenoma in 70% of available cases respectively. The latter was intrasellar in 44% of cases. Tumor size and extension were missing in 7.6% of cases.

The mean GH concentration at diagnosis was 31.1±37 μg/l. The median GH was 20 μg/l and IQR 10–36 μg/l.

Nadir GH after glucose load was reported in 861 patients; in only three patients (0.3%) it was lower than 1 μg/l. However, all these three patients showed typical clinical features, elevated IGF1, and a documented pituitary GH-secreting adenoma at surgery.

IGF1 serum levels were available at diagnosis in 1004 patients (66.4%). The mean value was 744±318 ng/ml. The median IGF1 as age-specific SDS was 8.53 (IQR: 5.82–12.34), without differences between men and women being observed.

Hyperprolactinemia was reported in 250/1310 patients (19%). It was observed more frequently in women than in men (65.7 vs 34.3%, $P<0.001$) and in macro- than in microadenomas (80.5 vs 19.5%, $P<0.001$). Nine patients had associated TSH hypersecretion and central hyperthyroidism.

At diagnosis, 392 (26%) patients had one or more pituitary deficiencies: 4.1% hypoadrenalism, 8.1% hypothyroidism, 16.4% hypogonadism, and 0.6% diabetes insipidus. All were adequately treated. Pituitary deficiencies were equally distributed between the two genders except for hypogonadism that was more frequent in men (24.2 vs 10.9%, $P<0.0001$). Smoking at the time of diagnosis was reported by 36% of patients, a share slightly greater than that reported for the general adult Italian population in the same years (about 30%) (18).

Comorbidities: diabetes mellitus and arterial hypertension

Diabetes mellitus was reported in 16.2% of cases, 139 women and 106 men with an age standardized rate of 12.4 and 16.2% respectively (*P*=NS). Diabetes mellitus was diagnosed at an earlier age than in the general population (Fig. 3A and B). A multivariate analysis considering age, gender, GH, and IGF1 serum levels at diagnosis and months of delay before diagnosis showed that older age, male gender, and higher IGF1 but not GH levels at baseline were significant predictors of diabetes (Table 1).

Hypertension affected 33% of acromegalic patients and was equally distributed between women and men (age-standardized rate: 33.7 vs 28.7% respectively, *P*=NS); however, it also appeared at younger age than in the normal population (Fig. 3C and D). A multivariate model considering age, gender, GH, and IGF1 serum levels at baseline and months of delay before diagnosis showed that older age and higher IGF1 levels at diagnosis were significant predictors of hypertension (Table 1).

Treatment

Several treatments are used to achieve cure in acromegaly, alone or in combination (Table 2).

Eighty percent of patients underwent surgical procedures. Pharmacotherapies were used in 75% of patients. The kind of medical therapy was reported in 720 cases: 74.6% (537/720) had been treated with short- or long-acting SSA, 10.3% (74/720) with dopamine agonists (DA) such as bromocriptine or cabergoline, 2.9% (20/720) with the GH receptor antagonist, and 12.2% (88/720) with both DA and SSA either sequentially or in combination. Radiotherapy was used in 18% (269/1512) of patients, with 14% of them (39/269) receiving two or more cycles. Radiosurgery, principally gamma knife, was used in 5.6% of the patients.

Only 34.4% of patients received one type of treatment, while 47.9% received two, 16.5% three, and 1.2% four. Patients who received only one type of treatment underwent surgery in 53% of cases, medical therapy in 46%, and radiotherapy in 1%.

Treatment choice was not different in patients bearing microadenomas vs macroadenomas and intrasellar vs extrasellar adenomas.

Disease-specific outcomes

The mean GH levels at the last follow-up were 4.9±15 μg/l (median: 2 μg/l; IQR: 1–3.8). In detail, GH levels decreased to <2.5 μg/l in 60.8% (below 1 μg/l in 21.6% of the entire cohort). Among the 695 patients who underwent a glucose load after therapy, 54.4% of them showed a nadir GH <1 μg/l.

At the last follow-up, IGF1 serum levels were available in 1321 patients (87% of the overall cohort). The mean value was 293±207 ng/ml and 802 patients (60.7%) achieved IGF1 levels within

the normal range. The median IGF1 SDS was 1.34 (IQR: 0.11–3.50); it was significantly higher in men than in women (1.95, IQR: 0.33–4.39 vs 1.11, IQR: 0.04–2.80 respectively; $P<0.05$).

Hyperprolactinemia persisted in 6.2% patients. At the last follow-up, patients who received pituitary conventional radiotherapy were more frequently hypothyroidal, hypoadrenal, and hypogonadal than patients who did not (62 vs 11%, 45 vs 10%, 57 vs 12%, $P<0.001$). At the last follow-up, 932/1427 patients (65%) were reported with controlled disease by the attending endocrinologist; among these, 55% (36% of the entire cohort) were off medical therapy. A recurrence after an initial remission was reported in 23 patients (2.4%).

Patients who achieved disease control had undergone surgery in 86% of cases vs 69% of patients with active disease.

A univariate model considering age, gender, GH, and IGF1 (expressed either as SDS or absolute value) at diagnosis, extension and size of the adenoma, delay of diagnosis, diabetes, hypertension, and hyperprolactinemia showed that male gender, extrasellar extension of the adenoma, highest GH levels at diagnosis, and diabetes were significant independent predictors of disease activity.

Mortality

By the end of 2002, 61 patients had died: 4.1% of men and 3.9% of women. The average age was 64±12 years (median: 66.5 years; IQR: 53.5–70.7 years) without differences between genders. Older age, higher GH at the last follow-up, higher IGF1 levels at diagnosis, malignancy, and conventional radiotherapy were independent predictors of mortality (Table 3). It is of note that superimposable results were obtained by expressing IGF1 as absolute values or as SDS.

Conventional external radiotherapy was also significantly associated with an increased morbidity for ischemic vascular diseases (35% in patients receiving radiotherapy vs 17% in the remainders, $P<0.005$). In our series, the prevalence of hypoadrenalism or hypogonadism was similar between the deceased and alive patients.

Main causes of death were vascular diseases and malignancies with similar prevalence. Twenty-three patients died from vascular diseases, 27.9% from cardiovascular, and 9.8% from cerebrovascular events. Women died more from stroke (20 vs 4%, $P<0.001$), while men from heart diseases (41 vs 28%, P=NS). The prevalence of death from malignancies was 36% (22/61) with no differences between genders. The cause of death was unknown in 12 patients.

The expected deaths were 53, which gives an SMR for the total cohort that is not significantly higher than the general Italian population (1.13; 95% CI, 0.86–1.46). SMR was 1.93 (95% CI, 1.34–2.70) in the subgroup of patients with persistently active disease as compared with 0.59 (95% CI, 0.37–0.90) in the patients with controlled disease.

Discussion

In the present epidemiological study, the first so far in Italy and one of the largest ever published, we have reported data on 1512 patients, representative of the acromegalic population in Italy. We assume to have included nearly the 45% of all the Italian acromegalic cases of that period, considering an Italian population of 57000000 inhabitants in 2002 and an estimated prevalence of

acromegaly of 60 per million (15). Like other retrospective studies involving a long period of time, our survey presents some difficulties in comparison of data collected across different centers. However, this is an inevitable trade-off to have the statistical power needed to answer important epidemiological issues.

The median age at diagnosis was 46 years, very similar to previous reports (11, 15, 19, 20, 21, 22). In our cohort, there was a prevalence of the female gender (59%) in agreement with most (9, 21, 22) even if not all cohorts (Table 4) (13, 20, 23, 24).

A higher prevalence of women was also described in one of the first epidemiological studies, published by Davidoff in 1926 (25). Both a diagnostic bias due to the greater awareness of women for their features and a real increased prevalence are possible explanations. However, it is of interest that men are more often diagnosed before the age of 45 years and women later on, as shown in Fig. 2, and in agreement with other series (21). Thus, a protective role of estrogen, delaying clinical presentation of acromegaly during the reproductive period, could be hypothesized, since it is well-known that estrogen reduces IGF1 concentrations in both normal and acromegalic women (26, 27, 28, 29).

The mean time delay for diagnosis was 6 years, which is similar to that reported in most recent series (13, 21, 22, 30). The time delay for diagnosis was 10–20 years in the 1960s (31), 9 years in the 1980s (23), and 6 years in the 1990s, but in the last 20 years it does not seem to have been shortened further (21); thus, acromegaly remains an underestimated disease (30, 31, 32, 33).

It is well-known that the prevalence of diabetes mellitus and hypertension is higher in acromegalic patients than in the general population. In our cohort, diabetes mellitus was reported in 16% of cases, with respect to 4.5% of the Italian population. However, we cannot exclude that we may have underestimated the real prevalence of the condition due to the retrospective nature of our study and since an oral glucose load was missing in a number of patients. As in the general population, the prevalence of diabetes increased with age, but starting at a younger age. In the literature, the prevalence of diabetes mellitus varies across a wide range, from 9 to 40% (Table 4) (8, 15, 19, 22). Besides differences due to genetic background, nutritional habits, age, BMI, and referral pattern, it has to be considered that diagnostic criteria were revised in the 1990s, making comparisons even more difficult. We confirmed that older age is an independent predictor of diabetes (22, 23), while higher GH levels and time delay for diagnosis were not, at variance with some previous observations (23). In addition, male gender appeared to be at greater risk of developing diabetes mellitus whereas no gender-related difference is evident in the general Italian population. It is remarkable that only IGF1 levels at diagnosis, and not GH, predicted the presence of diabetes. This is intriguing, considering both old studies in which IGF1 levels often reflected elevated fasting blood glucose in acromegaly (34) and very recent epidemiological studies showing that in the general population subjects with IGF1 levels in the upper normal range are at increasing risk of developing diabetes mellitus (35).

Also, the prevalence of hypertension varied remarkably across previous studies, from 18 to 60% (Table 4), with a mean prevalence of about 34% in a review collecting more than 2500 cases (36). Differences in diagnostic criteria and in techniques of blood pressure recording may explain most of the variability. In our series hypertension was found in 33% of patients, in comparison with 13.6% of the background population matched for gender and age. As in the general population, no gender difference was observed and the prevalence increased with age, so that nearly 50% of the acromegalic patients older than 55 years were hypertensive (Fig. 3C and D), both findings being consistent with previous observations (37). We also confirmed that hypertension, like diabetes, in the acromegalic population occurs not only more frequently, but also earlier than in the general

population. While higher GH levels at baseline were not an independent predictor of hypertension, IGF1 levels were, in keeping with a previous study (38). It is noteworthy that IGF1 has been implicated in the pathogenesis of essential hypertension (37, 39), even if the mechanisms involved are still not clarified (37). To further underline the importance of IGF1 in the development of comorbidities in acromegaly, as suggested by the pioneering work of Clemmons *et al*. (34), a recent paper showed that IGF1 normalization by pegvisomant resulted in a significant improvement of either hypertension or diabetes mellitus (40).

Treatment approach obviously changed during the long study period. In particular, medical therapies and radiosurgery became more frequent starting in the mid-1990s while conventional radiotherapy became progressively less used (11, 20). Most of our patients (80%) underwent surgery at some time, a figure similar to several studies (11, 13, 19, 21, 24).

Pharmacotherapy was used in about three-quarters of our patients while radiotherapy and radiosurgery in 23% of cases, a percentage similar to other series (20, 21, 24). Surprisingly, in our population there were no differences in the choice of first-line treatment on the basis of tumor size and extension; indeed, first-line treatment was surgical in 53.3% and medical in 45.9% of cases. To have a comparison with recent surveys, in the Belgian Registry (20) primary medical therapy was used in 23% and in the German Registry in 34% (21).

In our series, 65% of patients were considered in remission at the last follow-up. This figure reflects the results of years in which GH antagonist was not yet available, but SSAs had already entered clinical practice, and is comparable or even higher than other databases. The global cure or control rate reported in the Belgian (20) and in the West Midlands (9) databases were 49 and 46% respectively. In the Spanish Register, cure was reported in 31% (19) and in the Finnish database, either GH<2.5 μg/l or normal IGF1 was achieved by 55% of patients (11) (Table 4). As expected, however, these figures are lower than those reported by single centers of excellence (10). We observed that male patients with extrasellar adenomas, higher GH levels at diagnosis, and diabetes had the lowest probability of achieving control of their disease, all these factors being independent predictors.

It is well-known that untreated acromegaly is associated with a decreased life expectancy (4). In our series, 61 patients (4%) died during 10-year follow-up, compared with 53 expected, without differences between genders, at variance with other groups of patients with pituitary diseases. For example, among patients with hypopituitarism the mortality is greater in women (4).

The median age of death of our series (66 years) is similar to that reported by other European studies (9, 11, 20). In the total cohort the mortality for all causes was not significantly higher than in the general Italian population, while in the subgroup of patients who did not achieve full hormonal control it was increased by about twofold. These findings are in agreement with most (4, 8, 10, 19), even if not all (7, 13) recent series (Table 4). They confirm that the excess mortality associated with acromegaly can be greatly reduced by the modern management of the disease, which is able to successfully control hormonal hypersecretion in the majority of patients. However, it has to be considered that an analysis of mortality in these cohorts, including ours, is complex due to the low number of deaths by epidemiological standards (4) and the presence of other confounding factors such as the year of publication and differences among the populations of reference. In addition, due to the fact that only tertiary referral centers participated in the survey, mortality and morbidity rates were probably underestimated compared with the general Italian acromegalic population.

As in the general population, the main causes of death were found to be vascular diseases and malignancies. The reported prevalence of cerebrovascular death in acromegalic patients ranged

from 12 to 21% in the different series (7, 9, 19, 20), while in our population it occurred only in 9.8% of cases, mostly in females. The lower figure may be due to a limited use of conventional radiotherapy with respect to the oldest series. Cardiovascular death rate (27.8%) is comparable with data reported in Spanish (19) and Belgian registers (20), but is lower than in other European studies (1, 7, 9), and this likely reflects the lower cardiovascular mortality of the respective general populations (41). Conversely, death from malignancies (36%) was more frequent than that reported by other European surveys (7, 19, 20), and deserves further investigation.

Besides age at diagnosis and development of malignancy during follow-up, conventional radiotherapy (not including radiosurgery) and the last known GH value at follow-up were independent predictors of mortality, in keeping with other series (4, 9, 11). It may be expected that the new conformational techniques of radiotherapy could be less dangerous; however, the number of patients who underwent radiosurgery was too small to provide useful information about the possible link between this type of therapy and survival. Hypertension and diabetes mellitus were significant predictors of mortality only in univariate but not in multivariate analysis, in keeping with the original study by Bates *et al*. (6). This may be due to their tight correlation with age and IGF1 level at diagnosis. Interestingly, high IGF1 level at diagnosis was an independent predictor of mortality, whereas both basal GH concentrations and the last IGF1 concentrations were not. In this context, it is worth recalling that in the 1980s IGF1 levels were considered by many experts the best marker of severity of the acromegalic disease (34). A strength of our study is the large number of acromegalic patients in whom IGF1 levels were available at diagnosis and this may explain why previous studies including a limited data set were not able to demonstrate a predictive role for IGF1 (1, 3, 6, 7, 8, 9, 10, 13). The limitation that IGF1 levels have been measured by different assays was circumvented by comparing them with those of the largest Italian database, the one of the University of Genoa, thus allowing us to express IGF1 also as SDS in the statistical analysis. Since we have obtained superimposable results with rough values or SDS, we think that our conclusions are not significantly affected by this limitation.

In conclusion, we have confirmed that diabetes mellitus and hypertension are more frequent and peak much earlier in acromegaly than in the background population. We have shown that male patients with extrasellar adenomas, high GH levels at diagnosis, and diabetes mellitus have the lowest probability of achieving control of their disease. We have confirmed the deleterious effects of conventional radiotherapy and the lack of a complete control of GH hypersecretion, but also shown that modern management of the disease is associated with an almost normal life span.

However, we have not been able to confirm that the last known IGF1 level is an independent predictor of mortality, while we have shown for the first time the importance of IGF1 levels at diagnosis in causing morbidity and long-term mortality.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Figure legends:

Figure 1: Percentage distribution of patients throughout Italy.

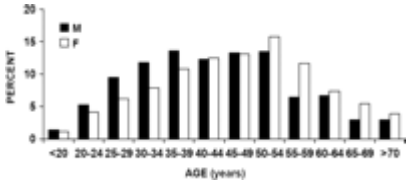

Figure 2: Distribution of acromegalic patients according to gender (males, closed bars; females, open bars) and age group at diagnosis.

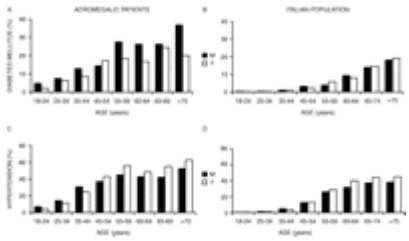

Figure 3: Percentage prevalence of diabetes mellitus (A and B) and hypertension (C and D) in the acromegalic population in respect to the Italian general population (B and D) according to age groups and gender (males, closed bars; females, open bars).